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Original Article

A QSAR study of some Phenoxyacetamide derivatives as a MAO-A inhibitor

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ABSTRACT: Antidepressants are the most prescribed therapy for depression. The prevailing theory is that antidepressants increase the concentration of one or more brain chemicals (neurotransmitters) that nerves in the brain use to communicate with one another. The neurotransmitters affected by antidepressants are norepinephrine, serotonin, and dopamine. In order to address the need for new MAO inhibitors with less side effects, we can aim compounds previously discovered for their potential as MAOIs. Among them, safinamide was reported to be a potent anti-MAO B agent, and milacemide, which was found to be a potent MAO inhibitor and a prodrug for glycine. The present work deals with the aim because Currentely available MAO inhibitors {Isocarboxazid (Marplan), Phenelzine (Nardil), Selegiline (Emsam), Tranylcypromine (Parnate) etc} develop side effects because they do not selectively for MAO-A and MAO-B. So, the present study is focused to develop potent selective MAO-A inhibitors, to treat depression, that may be of better pharmacological activity with less adverse effect.

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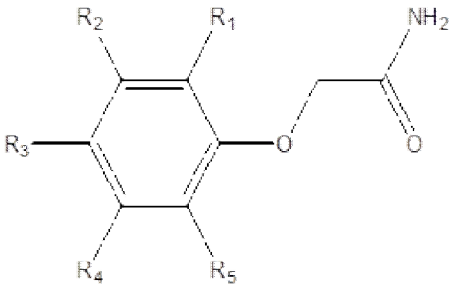
INTRODUCTION

Now a day, the entire pharmaceutical industry is faced with the challenge of increasing productivity and innovation. The major hurdles are the increasing costs of research and development and a simultaneous stagnating number of new chemical entities (NCEs).

For several thousand years, man has used herbs and potions as medicines, but it is only since the mid-nineteenth century that serious efforts were made to isolate and purify the active principles of these remedies and Medicinal chemistry received further boost in 1940 as pharmacology, which until then had been dominated by physiology, became increasingly biochemical in character with new understanding of the role of enzymes and cell receptors. Successful drug synthesis depends upon the ability to identify new chemical entities that have potential to treat diseases in a safe and efficient manner.

In order to address the need for new MAO inhibitors with less side effects, we can aim compounds previously discovered for their potential as MAOIs. Among them, safinamide was reported to be a potent anti-MAO B agent, and milacemide, which was found to be a potent MAO inhibitor and a prodrug for glycine [1-5, 32, 33].



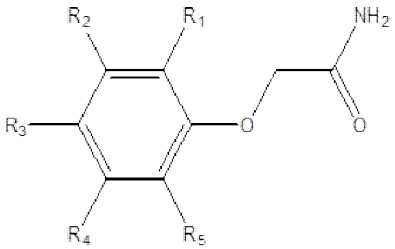
2-Phenoxyacetamide

According to Wei *et al*., several substitutions are possible at R1-R5 and which can affect the MAO inhibitory activity of enzyme and gives a variety of compounds with satisfactory MAO activity. Results of this study show that most of the synthesized compounds are potent and selective inhibitors of MAO-A rather than of MAO-B.

Selection of series of Phenoxyacetamide [6-9, 34]

For the QSAR study to target MAO enzyme selection of series is based on IC_{50} value. The ratio of Maximum and minimum IC50 value should be ≥ 1000. The following series of Phenoxyacetamide is selected on the same basis.

– First eighteen compounds

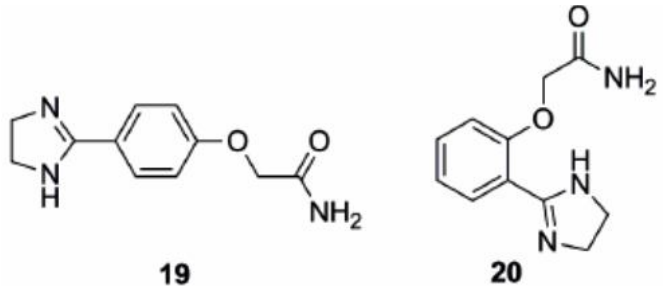


2-Phenoxyacetamide

1: $R_1=R_2=R_3=R_4=R_5=H$, X=O;
2: 2-naphthalenyl, X=O;
3: $R_1=R_2=R_4=R_5=H$, $R_3=F$, X=O;
4: $R_1=R_2=R_4=R_5=H$, $R_3=Cl$, X=O;
5: $R_2=R_4=R_5=H$,$R_1=Cl$, X=O;
6: $R_1=R_2=R_4=R_5=H$,R_3=-CHO, X=O;
7:$R_2=R_4=R_5=H$,R_1=-CHO, X=O;
8:$R_1=R_4=R_5=H$,$R_2=R_3$=-CH_3, X=O;
9:$R_2=R_4=R_5=H$,R_1=-CH_3,X=O
10:$R_1=R_2=R_4=R_5=H$,R_3=-CH_3, X=O
11: $R_2=R_3=R_4=R_5=H$, R_1=-OCH_3, X=O;
12: $R_1=R_2=R_4=R_5=H$, R_3=-OCH_3, X=O;
13: R_2= $R_3=R_4=R_5=H$, R_1=-COOH, X=O;
14: $R_2=R_3=R_4=R_5=H$, R_1=-$COOCH_3$, X=O;
15:$R_1=R_2=R_4=R_5=H$,R_3=-$NHCOOC(CH_3)_3$, X=O;
16:$R_1=R_2=R_4=R_5=H$,R_3=-$NHCOCH_3$, X=O;
17:$R_1=R_2=R_3=R_4=R_5=H$, X=S
18:$R_1=R_4=R_5=H$,$R_2=R_3$=-CH_3, X=S

Table 1. Monamine oxidase inhibitory activity of compounds **1–28** [a].

Item	R	X	IC_{50} (μM)		SI [b]
			MAO-A	MAO-B	
1	Phenyl	O	69	778	11.27
2	2-Naphthalenyl	O	149	542	3.64
3	4-Fluoro-phenyl	O	92	255	2.77
4	4-Chloro-phenyl	O	490	202	0.41
5	2-Chloro-phenyl	O	98	694	7.08
6	4-Formyl-phenyl	O	89	457	5.13
7	2-Formyl-phenyl	O	142	559	3.94
8	3,4-Dimethyl-phenyl	O	113	534	4.73
9	2-Methyl-phenyl	O	26	663	25.5
10	4-Methyl-phenyl	O	3	541	180
11	2-Methoxy-phenyl	O	96	775	8.07
12	4-Methoxy-phenyl	O	4	980	245
13	o-Carboxyphenyl	O	217	177	0.82
14	o-Acid ester	O	108	98	0.91
15	4-(*N*-tert-Butyl *O*-acyl)amine-phenyl	O	196	296	1.51
16	4-(*N*-acetyl)amine- phenyl	O	61	553	9.07
17	Phenyl	S	166	642	3.87
18	3,4-Dimethyl-phenyl	S	292	366	1.58
19	4-(4,5-dihydro-1H-imidazol-2-yl)-phenyl	O	61	506	8.30
20	2-(4,5-dihydro-1H-imidazol-2-yl)-phenyl	O	186	714	3.84
21	4-((Prop-2-ynylimino)methyl)-phenyl	O	0.018	0.076	4.22
22	4-((Prop-2-ynylamino)methyl)-phenyl	O	0.094	0.164	1.74
23	4-((benzylimino)methyl)-phenyl	O	96	575	5.99
24	4-((benzylamino)methyl)-phenyl	O	37	534	14.43
25	2-((Prop-2-ynylimino)methyl)-phenyl	O	0.068	0.176	2.59
26	2-((Prop-2-ynylamino)methyl)-phenyl	O	0.168	0.188	1.19
27	2-((benzylimino)methyl)-phenyl	O	147	562	3.82
28	2-((benzylamino)methyl)-phenyl	O	107	497	4.64
	Clorgyline		0.0011 (0.0014)		
	Pargyline			0.0035 (0.0038)	



19 20

The discovery of a lead compound is assumed to be the most complicated aspect of the drug scheming process. Once a lead compound for a novel therapeutically vigorous drug has been revealed, it is additionally subjected to effectual toxicological studies so that its worth and protection can be thoroughly evaluated before the instigation of its clinical trials [35].

MATERIALS AND METHODS

A series of phenoxyacetamide derivatives was selected from a reported article which presented the synthesis of novel derivatives of this compound and evaluated their MAO A and MAO B inhibitory activity. Structure build-up, physico-chemical property determination, and sequential multiple regression analysis was performed on the reported series. In QSAR study all computational work was performed using ChemDraw2D Ultra8.0 and Chem3D Ultra 8.0 software core i3 Duo processor and a windows7 Operating system. The regression analysis was carried out using VALSTAT software.

EXPERIMENTAL WORK

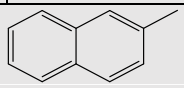
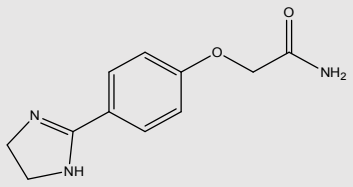
QSAR Study of Selected Series of Compounds

The QSAR paradigm is based on the assumption that there is an underlying relationship between the molecular structure and biological activity. On this assumption QSAR attempts to establish a correlation between various molecular properties of a set of molecules with their experimentally known biological activity. Determination of QSAR generally proceeds as follows:

Biological Activity Calculation

Several substitutions were carried out on Phenoxyacetamide ring and 28 compounds were synthesized and their inhibitory potency towards monoamine oxidases A (MAO-A) and B (MAO-B) were evaluated using enzyme and cancer cell lysate. 2-(4 Methoxyphenoxy) acetamide and (2-(4-((prop-2ynylimino) methyl)phenoxy) acetamide were successfully identified as the most specific MAO-A inhibitor, and the most potent MAO-A/-B inhibitor, respectively [10-14]. The MAO A inhibitory activity data IC_{50} values were determined against MAO A subunit of synthesized compounds of series were converted to pIC_{50}. The MAO A inhibitory activity of synthesized compounds was determined in terms of MIC against *isoenzyme*. The MIC is expressed as micro Molar concentration(C) and converted into – log C values (called as biological activity). These dependent data are tabulated in the Tables 2 and 3.

Table 2: Dependent data used for QSAR study for MAO A inhibitory activity (1-20)

Compounds	R_1	R_2	R_3	R_4	R_5	X	IC_{50} (µM)	Biological Activity
1	H	H	H	H	H	O	69	4.1611
2						O	149	3.8268
3	H	H	F	H	H	O	92	4.0362
4	H	H	Cl	H	H	O	490	3.3098
5	Cl	H	H	H	H	O	98	4.0087
6	H	H	CHO	H	H	O	89	4.0506
7	CHO	H	H	H	H	O	142	3.8477
8	H	CH_3	CH_3	H	H	O	113	3.9469
9	CH_3	H	CH_3	H	H	O	26	4.5850
10	H	H	CH_3	H	H	O	03	5.5228
11	O CH_3	H	H	H	H	O	96	4.0177
12	H	H	O CH_3	H	H	O	04	5.3979
13	COOH	H	H	H	H	O	217	3.66355
14	$COOCH_3$	H	H	H	H	O	108	3.9665
15	H	H	$NHCOOC(CH_3)_3$	H	H	O	196	3.7077
16	H	H	$NHCOCH_3$	H	H	O	61	4.2146
17	H	H	H	H	H	S	166	3.7798
18	H	H	CH_3	H	H	S	292	3.5346
19.							61	4.2146

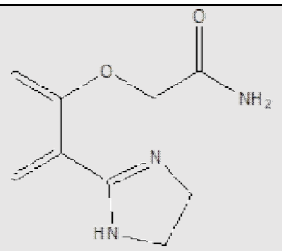
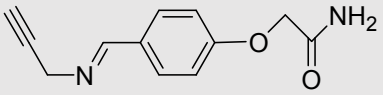
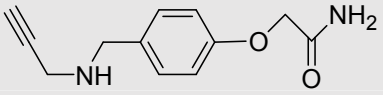
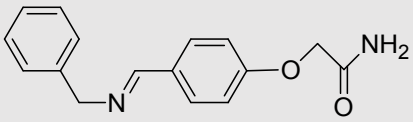
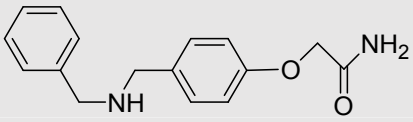
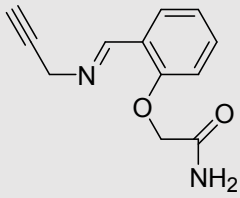
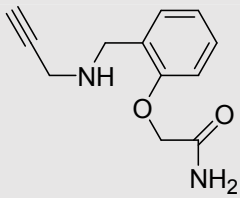
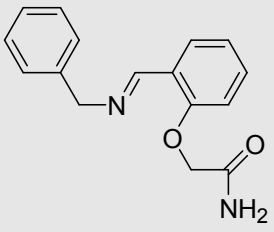
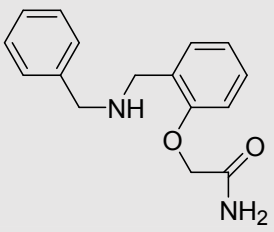
20.		186	3.7304

Table 3: Dependent data used for QSAR study for MAO A inhibitory activity (20-28)

Compound	Structure	IC_{50} (µM)	Biological Activity
21		0.018	7.7447
22		0.094	7.0268
23		96	4.0177
24		37	4.4317
25		0.068	7.1674
26		0.168	6.7746
27		147	3.8326
28		107	3.9706

Determination of Molecular Descriptors

The structures of the remaining twenty-four compounds were fabricated by means of Chemdraw Ultra 7.0.1 of Chemoffice Ultra 7.0.1 suite software, which is a product of Cambridge soft corporation, U.S.A. These structures were then saved in MDL (mol) format which is followed by energy minimization using Chem3D ultra 7.0.1 by the means of MM2 (Molecular Mechanics) force fields and followed by MOPAC-Closed shell (AM-1) pro force fields using 0.100 as root mean square gradient.

The minimization was executed until the Root Mean Square (RMS) gradient value reaches a value smaller than 0.1kcal / mol. The minimized molecules were subjected to reoptimization via Austin model-1 method until RMS gradient attains a value smaller than 0.0001 kcal / mol A° using MOPAC. The geometry optimization of the lowest energy structure was carried out using Eigenvector Following (EF) routine. The descriptor values for all the molecules were calculated using "compute properties" module of program [15-21].

The properties of all these compounds were simultaneously computed using Chem3D ultra. Subsequently, all these calculated properties were arranged in Microsoft Excel 2007 sheet and subjected to the statistical software VALSTAT.

Selection of Training and Test Set:

The compounds were divided into training and test sets by random selection. The training set was used for the model development and the test set was used for cross validation of QSAR model developed by the training set. The data of 28 molecules was randomly into training set of 22 compounds (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 19, 22, 23, 24, 25, 26, 27, 28) and test set of 6 compounds (1, 16, 17, 18, 20, 21) for multiple linear regression model using log1/Ic_{50} activity as dependent variable and various 2D descriptors as independent variables [22-28].

QSAR Models Development

A set of 28 compounds were selected from the report obtained from the MAO-A inhibitory activity and divided as training set and test set each consisting of 22 and 6 compounds respectively by random selection method. The descriptors were used in this study are given along with values in the Table 4.

QSAR Model 1

BA= [3.73764(±1.82156)] +pc [-1.12149(±0.335012)] +be [-0.096964(±0.0405414)] +sc [2.9265(±1.88014)]

n=22, r=0.692907, r^2=0.48012, variance=0.77052, std= 0.877793, F=5.54112, Q^2= 0.25059, Spress = 1.0539, r^2pred = 0.278751

QSAR Model 2

BA= [5.3987(±0.917169)] +caa [0.00264657(±0.00185923)] +pc [-1.03793(±0.327816)] +be [-0.108387(±0.0393591)]

n=22, r=0.685439, r^2=0.469826, variance=0.785776, std= 0.88644, F=5.31704, Q^2 = 0.208232, Spress = 1.08328, r^2pred= 0.256099

QSAR Model 3

BA= [5.1416(±1.27483)] +cma [0.00679232(±0.00597503)] +pc [-1.15213(±0.365385)] +be [-0.106365(±0.0406552)]

n=22, r=0.670563, r^2=0.449655, variance=0.815672, std= 0.903146, F=4.90225, Q^2 = 0.162244, Spress = 1.11429, r^2pred= 0.301534

QSAR Model 4

BA= [5.45628(±0.946519)] +caa [0.00480994(±0.00217723)] +se [-0.338721(±0.124616)] +1,4ve [-0.33031(±0.117859)]

n=22, r=0.661066, r^2=0.437009, variance=0.834415, std= 0.913463, F=4.65736, Q^2 =0.211758, Spress = 1.08086, r^2pred = -0.548193

QSAR Model 5

BA= [2.85869(±1.76879)] +pc [-0.969545(±0.343327)] +se[-0.239747(±0.121902)] +sc [3.45088(±1.91372)]

n=22, r=0.660365, r^2=0.586081, variance=0.835789, std= 0.914215, F=4.63983, Q^2 = 0.0692081, Spress = 1.17454, r^2pred= 0.623923

Validation of Model and Prediction of Biological Activity: Validation of model was done in two steps:

A. External validation

B. Internal validation

A. **External validation**: the model was validated by VALSTAT software, randomly making 22 compounds (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 19, 22, 23, 24, 25, 26, 27, 28) of training set and 6 compounds (1, 16, 17, 18, 20, 21) of test set.

B. **Internal validation:** The VALSTAT software automatically performed leave one out methods to get best model to increase biological activity. QSAR model was developed and this model was used to predict the biological activity of test set of compounds.

RESULT AND DISCUSSION

Statistical data of 5 models given in table 6. For all models training set (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 19, 22, 23, 24, 25, 26, 27, 28) of compounds and test set (1, 16, 17, 18, 20, 21) of compounds were taken randomly by VALSTAT software computer program and intercorrelation limit was used at 0.5. Out of all 5 models, model 5 was selected based on high value of stastical data Q2, r2 and r2 prediction.

Table 4 Descriptors of Compounds of Selected Series Calculated for QSAR Study

Compound	caa	Cma	csev	pmix	pmiy	pmiz	Mr	pc	se	be	sbe	tvc	Mti	svd	sa	sc	tc	te	1,4ve	nl,4ve
1	327.502	153.716	117.166	143.427	986.534	1117.420	4.174	0.556	2.451	8.060	-0.062	0.001	1302	40.000	9.091	0.750	0.029	-3.687	4.307	0.019
2	396.681	197.873	157.269	270.271	2000.470	2177.880	5.862	1.730	2.259	5.692	-0.008	0.000	2950	54.000	13.067	0.800	0.005	-10.512	6.598	2.378
3	336.325	158.673	121.081	147.445	1398.930	1495.750	4.182	0.839	3.316	6.542	-0.121	0.000	1518	48.000	10.083	1.000	0.024	-1.197	3.779	-0.815
4	3.519	168.759	131.441	151.092	1760.740	1857.090	4.565	1.409	2.625	8.198	-0.080	0.001	1518	41.778	10.083	1.000	0.024	-2.745	4.607	-0.614
5	343.951	165.745	132.456	389.850	942.245	1229.830	4.565	1.179	2.881	8.837	-0.068	0.001	1478	41.778	10.083	0.750	0.024	-3.761	4.776	-2.321
6	356.496	172.070	133.471	152.931	1718.130	1718.130	4.573	0.274	2.663	9.947	-0.079	0.000	2001	50.000	11.769	0.800	0.017	-2.725	5.043	-1.890
7	343.772	169.923	134.930	341.604	971.523	1286.120	4.573	0.274	2.806	9.403	-0.069	0.000	1881	50.000	11.769	0.750	0.017	0.690	5.070	-2.493
8	381.518	189.000	150.388	240.928	1469.260	1610.500	5.101	1.504	2.903	8.040	-0.081	0.001	2023	44.000	11.769	1.000	0.020	-3.691	6.023	-0.755
9	349.234	169.211	135.175	298.723	829.542	1618.070	4.538	1.055	2.825	9.342	-9.756	0.001	1598	42.000	10.833	0.754	0.024	-5.406	5.054	-2.072
10	359.611	173.291	134.088	148.729	1337.700	1465.610	4.538	1.055	2.881	7.435	0.080	0.001	1668	42.000	10.833	1.000	0.024	-2.407	4.771	-0.527
11	359.930	178.001	143.925	349.090	952.490	1232.490	4.791	0.293	3.360	15.051	0.071	0.000	1901	48.000	11.077	0.750	0.017	-1.801	6.688	-3.209
12	375.796	181.736	141.110	158.117	1745.330	1847.630	4.791	0.643	3.261	13.932	-0.107	0.000	2021	48.000	11.077	0.800	0.017	1.214	6.453	-0.200
13	350.100	173.987	138.802	479.420	1032.500	1481.540	4.826	0.089	3.049	15.318	-0.176	0.000	2172	56.000	12.071	0.750	0.014	-2.020	4.080	-5.744
14	393.201	197.962	158.490	673.841	1114.450	1750.180	5.290	0.540	3.718	18.096	-0.086	0.000	2672	58.000	13.067	1.000	0.010	0.084	8.144	5.306
15	505.088	260.883	217.263	312.056	4909.450	5011.820	7.050	1.390	7.983	20.557	0.232	0.000	5993	68.000	17.053	1.000	0.003	-2.971	5.109	-0.691
16	412.534	203.146	157.934	223.573	2525.330	2720.020	5.506	-0.269	6.482	7.807	0.150	0.000	3043	56.000	13.067	1.000	0.010	1.491	3.408	1.474
17	341.876	163.930	130.768	188.878	1124.370	1212.560	4.827	0.991	0.163	0.522	0.034	0.003	1302	34.657	9.091	0.750	0.029	-6.623	2.087	-1.630
18	396.027	199.468	164.271	281.965	1689.040	1835.820	5.755	1.939	0.404	6.891	0.021	0.002	2023	38.657	11.077	1.000	0.020	-8.173	3.319	-1.869
19	425.885	213.007	168.864	213.842	2954.910	3150.790	6.100	1.057	0.633	6.255	0.049	0.000	3622	58.000	14.063	1.000	0.003	4.682	4.758	1.097
20	407.195	206.477	173.123	766.153	1059.630	1584.870	6.100	1.057	6.908	6.253	0.059	0.000	3292	58.000	14.063	1.000	0.003	0.225	4.627	1.207
21	446.394	220.625	172.104	230.801	3305.130	3403.770	6.169	0.180	0.559	3.811	6.123	0.000	4053	58.000	14.063	1.000	0.007	-6.679	6.397	-3.865
22	451.629	225.193	179.101	254.718	3265.610	3428.290	6.195	0.524	0.565	3.234	0.087	0.000	4053	56.000	14.063	1.000	0.006	-4.831	5.342	-4.725
23	521.935	269.292	220.113	487.454	5225.810	5476.670	7.956	2.248	0.700	4.649	0.129	0.000	7761	70.000	18.050	1.000	0.001	12.853	10.222	-4.896
24	525.455	274.811	230.003	493.196	5205.580	5394.050	7.981	1.082	0.726	2.216	0.047	0.000	7761	68.000	18.050	1.000	0.001	-7.350	9.161	-4.182
25	434.400	215.797	173.279	730.401	1483.320	1962.650	6.169	0.180	0.763	4.474	0.147	0.000	3713	58.000	14.063	1.000	0.006	-5.368	6.289	-5.557
26	424.272	215.628	183.687	782.140	1294.670	1751.170	6.195	0.524	0.634	2.399	0.054	0.000	3713	56.000	14.063	1.000	0.006	-2.733	3.157	8.585
27	503.239	264.327	224.875	855.542	2784.670	3263.160	7.956	2.248	0.877	3.555	0.131	0.000	7141	70.000	18.050	1.000	0.001	-7.321	9.921	-2.922
28	470.826	254.748	237.111	946.545	2082.300	2596.110	7.981	1.082	0.875	3.332	0.060	0.000	7141	68.000	18.050	1.000	0.001	-11.111	9.444	1.214

Table 5 Intercorrelation Matrix of Descriptors

	Caa	cma	csev	pmix	pmiy	pmiz	mr	pc	se	be	sbe	tvc	mti	Svd	sa	sc	Tc	te	1,4ve	nl,4ve
caa	1																			
cma	0.7358	1																		
csev	0.7187	0.986	1																	
pmix	0.4641	0.5687	0.6509	1																
pmiy	0.5544	0.8327	0.7579	0.06	1															
pmiz	0.6015	0.878	0.8115	0.1662	0.9895	1														
mr	0.7076	0.9844	0.9882	0.6338	0.7719	0.8234	1													
pc	0.1776	0.4762	0.4505	0.0594	0.5089	0.5118	0.5045	1												
se	0.1849	0.2749	0.2838	0.3869	0.0712	0.105	0.3747	0.0731	1											
be	0.1855	0.3198	0.3319	0.2682	0.1852	0.193	0.4144	0.2891	0.86	1										
sbe	0.1172	0.2388	0.2179	0.1116	0.236	0.1619	0.2258	0.015	0.0637	0.0483	1									
tvc	0.6824	0.6466	0.6308	0.4953	0.4763	0.5095	0.6349	0.0941	0.2319	0.0994	0.3819	1								
mti	0.7132	0.9807	0.9801	0.59	0.8162	0.8632	0.9861	0.4922	0.3183	0.3653	0.2215	0.6379	1							
svd	0.7397	0.9221	0.9163	0.6361	0.732	0.7848	0.917	0.3066	0.2207	0.18	0.3121	0.8428	0.9305	1						
sa	0.7521	0.9818	0.9834	0.6328	0.7761	0.8296	0.9843	0.4334	0.2919	0.3149	0.2298	0.7116	0.9844	0.9593	1					
sc	0.2395	0.572	0.5439	0.2771	0.4879	0.4901	0.5342	0.3558	0.2385	0.3779	0.3386	0.2482	0.5176	0.4551	0.513	1				
tc	0.735	0.896	0.8831	0.6077	0.6752	0.7233	0.9014	0.2638	0.3666	0.2947	0.3289	0.8587	0.8635	0.9318	0.916	0.4378	1			
te	0.0314	0.0701	0.1417	0.2134	0.1665	0.1492	0.132	0.0341	0.1275	0.2637	0.1046	0.0173	0.046	0.0188	0.0899	0.0201	0.1469	1		
1,4ve	0.5144	0.6963	0.7011	0.5234	0.4924	0.5447	0.7259	0.4945	0.3137	0.2075	0.1336	0.3974	0.741	0.6602	0.71	0.2583	0.5909	0.0377	1	
nl,4ve	0.0654	0.0289	0.0212	0.1953	0.2023	0.1894	0.0192	0.0809	0.0739	0.0101	0.0329	0.0021	0.0836	0.0451	0.0331	0.2811	0.0567	0.1747	0.1512	1

Table 6 Statistical Data for Developed QSAR Models

Model No.	Number of Data point (n)	Correlation Coefficient (r)	Coefficient of determination (r^2)	Cross validated r^2 (Q^2)	r^2pred	Standard deviation (Std)	Spress (Standard error for prediction)
1.	22	0.692907	0.48012	0.25059	0.278751	0.877793	1.0539
2.	22	0.685439	0.469826	0.208232	0.256099	0.88644	1.08328
3.	22	0.670563	0.449655	0.162244	0.301534	0.903146	1.11429
4.	22	0.661066	0.437009	0.211758	-0.548193	0.913463	1.08086
5*.	22	0.660365	0.586081	0.692081	0.623923	0.914215	1.17454

Model no. 5 shows descriptors partition coefficient, stretch energy and shape coefficient are positively correlated with biological activity of compounds. When increased the value of both descriptors it will be increased biological activity of compounds.

Final correlation matrix is given in table 9. Observed, calculated, residual, predicted residual values for training set of compounds and observed, predicted, predicted residual values for test sat of compounds is given in table 7 and 8 respectively.

Graph between observed values and calculated values, observed values and predicted values for training set of compounds is given in figure 1 and 2 respectively. Graph for test set of compounds plotted between observed values and predicted values is given in figure 3.

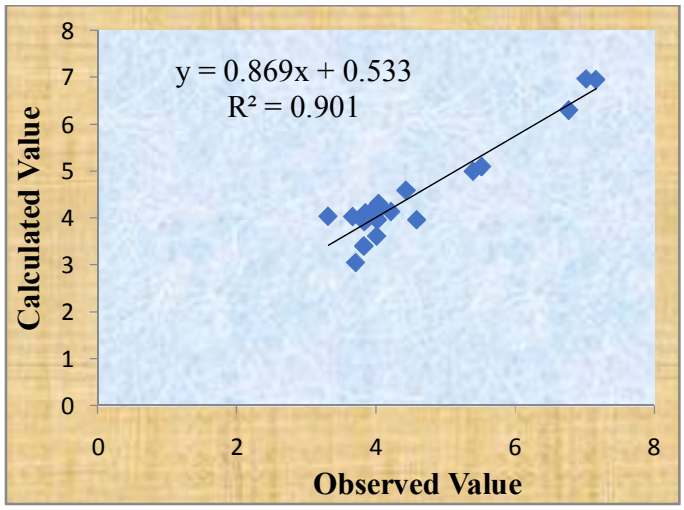


Fig. 1: Graph between Observed and Calculated Values for Training Set of Compounds

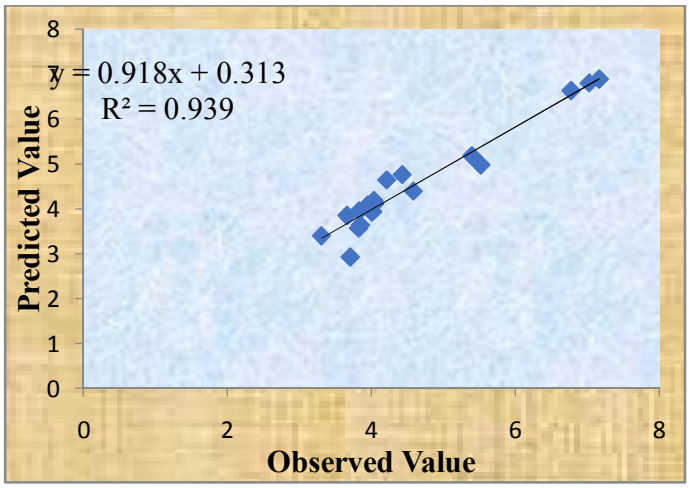


Fig. 2: Graph between Observed and Predicted Values for Training Set of Compounds

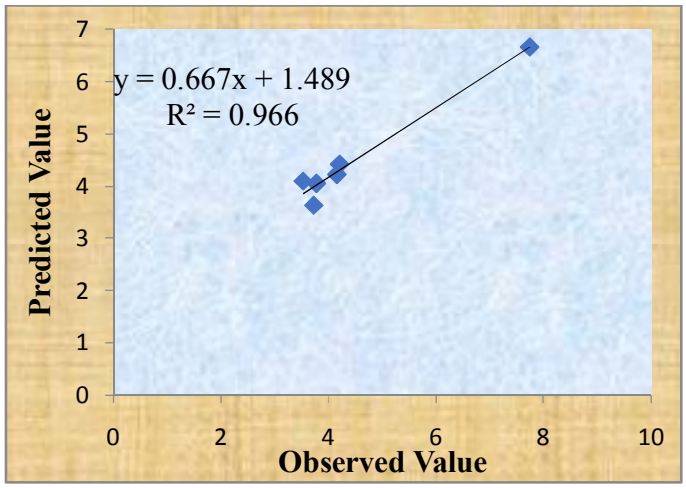


Fig. 3: Graph between Observed and Predicted Values for Test Set of Compounds

Table 7: Observed, Calculated, Predicted, Calculated Residual and Predicted Residual Values for Training set of Compounds

S. No.	Compounds	Observed values	Calculated values	Calculated Residual values	Predicted values	Predicted Residual values
1.	2	3.8268	3.4004	0.42639	3.5672	0.2596
2.	3	4.0362	4.301	-0.26483	4.1833	-0.14714
3.	4	3.3098	4.0341	-0.72433	3.4015	-0.0917
4.	5	4.0087	3.6131	0.39561	3.9226	0.08608
5.	6	4.0506	4.2155	-0.1649	4.1107	-0.06009
6.	7	3.8477	4.1086	-0.26088	3.6394	0.20834
7.	8	3.9469	4.1553	-0.20841	4.0792	-0.13225
8.	9	4.5850	3.9605	0.62452	4.3987	0.18635
9.	10	5.5228	5.0959	0.4269	4.9819	0.54094
10.	11	4.0177	4.1552	-0.13747	4.1222	-0.10451
11.	12	5.3979	4.9923	0.40561	5.181	0.21695
12.	13	3.66355	4.03	-0.36645	3.8556	-0.19204
13.	14	3.9665	4.0947	-0.12818	4.0825	-0.11599
14.	15	3.7077	3.0485	0.65922	2.9277	0.78005
15.	19	4.2146	4.1329	0.0817	4.6452	-0.43055
16.	22	7.0268	6.9662	0.06064	6.8031	0.22375
17.	23	4.0177	3.9622	0.05547	3.9402	0.07752
18.	24	4.4317	4.5865	-0.15475	4.7624	-0.3307
19.	25	7.1674	6.952	0.21537	6.8956	0.27176
20.	26	6.7746	6.2994	0.47516	6.6376	0.13696
21.	27	3.8326	3.9198	-0.08722	3.953	-0.12043
22.	28	3.9706	4.0507	-0.08012	4.067	-0.09636

Table 9: Observed, Predicted and Predicted Residual Values for Test set of Compounds

Compounds	Observed value	Predicted value	Residual values
1	4.1611	4.2201	-0.05897
16	4.2146	4.4159	-0.20131
17	3.7798	4.0469	-0.26706
18	3.5346	4.0925	-0.55788
20	3.7304	3.6286	0.10177
21	7.7447	6.6598	1.0849

Table 10: Correlation Matrix of Model

	pc	se	sc
Pc	1		
Se	0.073053	1.000000	
Sc	0.355831	0.238467	1.000000

pc = partition coefficient; se = stretch energy; sc = shape coefficient

CONCLUSION

QSAR study was performed on all compounds against MAO- A inhibitors using CHEM DRAW software version 7.0. For all compounds the descriptor/parameter values were calculated by "compute" properties program. The Regression Analysis was carried out using VALSTAT software.

The best model was selected on the basis of Statical Parameters like r, r^2, q^2, pred. r^2, standard deviation, spress. From the QSAR study concluded that partition coefficient and 1,4vander wall energy both is positively correlated to activity. It should be attached to the molecules to increase the Biological Activity. Based on best model, we can design new compound to improve activity.

REFERENCES:

1. John Smith H (2006) Introduction to the Principles of Drug Design and Action, 4th Edition. CRC Press, New York, pp 78-80.
2. Eggenweiler HMV (1985) Int J Immunopharmacol. *7*: 655-660
3. Gomoll AW, Temple DL (1987) Drug Dev Res. 10: 57-62.
4. Povl KL, Tommy L, Ulfa H (2004) Text Book of Drug Designand Discovery. Taylor and Franchis Inc, New York, pp 16-20.
5. Tipton KF (1986). Enzymology of monoamine oxidase. Cell Biochem Funct 4: 79-87.
6. Rang HP, Dale MM, Ritter JM, Flower RJ (2008) Pharmacology. Churchill Vingstone Elsevier: London, p 174.
7. Youdim MBH, Edmondson D, Tipton KF (2006) The therapeutic potential of monoamine oxidase inhibitors. Nat Rev Neurosci 7:295–309. [PubMed: 16552415]
8. Shih JC, Chen K, Ridd MJ (1999) Monoamine oxidase: From genes to behavior. Annu Rev Neurosci 22:197–217. [PubMed: 10202537]
9. Edmondson DE, Mattevi A, Binda C, Li M, Hubalek F(2004) Structure and mechanism of monoamine oxidase. Curr Med Chem 11:1983–1993. [PubMed: 15279562]
10. Youdim MB, Bakhle YS (2006) Monoamine oxidase: isoforms and inhibitors in Parkinson´s disease and depressive illness. Br J Pharm 147, S287-S296
11. Geha RM, Chen K, Wouters J, Ooms F, Shih JC (2002) Analysis of conserved active site residues in monoamine oxidase A and B and their three-dimensional molecular modeling. J Biol Chem 277, 17209-17216.
12. Guay DR (2006) Am J Geriatr Pharmacother. 4: 330-39.
13. Riederer P, Danielczyk W, Grunblatt E (2004) Neurotoxicology. 25: 271.
14. Fernandez HH, Chen J (2007). J Clin Neuropharmacol. 30: 150.
15. Johnston JP (1968) some observations upon a new inhibitor of monoamine oxidase in brain tissue. Biochem Pharmacol 17: 1285e1297.
16. Bach AW, Lan NC, Johnson DL, Abell CW, Bembenek ME, Kwan SW, Seeburg PH, Shih JC (1988) cDNA cloning of human liver monoamine oxidase A and B: molecular basis of differences in enzymatic properties. Proc Nat Acad Sci 85: 4934e4938.
17. Colibus LD, Li M, Binda C, Lustig A, Edmondson DE, Mattevi A (2005) Proceedings of the National Academy of Sciences of the United States of America 102: 12684e12689.
18. Binda C, Hubálek F, Edmonson DE, Mattevi A (2002) Nature Structural Biology 9: 22e26.
19. Ma J, Yoshimura M, Yamashita E, Nakagawa A, Ito A, Tsukihara T (2004) J Mol Biol. 338: 103 –114.
20. Son SY, Ma J, Kondou Y, Yoshimura M, Yamashita E, Tsukihara T (2008) Structure of human monoamine oxidase A at 2.2-_A resolution: the control of opening the entry for substrates/inhibitors. Proc Natl Acad Sci 105 : 5739e5744.
21. Binda C, Wang J, Pisani L, Caccia C, Carotti A, Salvati P, Edmondson DE, Mattevi A (2007) Structures of human monoamine oxidase B complexes with selective noncovalent inhibitors: safinamide and coumarin analogs. J Med Chem 50: 5848e5852.
22. Youdim MB, Edmondson DE, Tipton KF (2006) The therapeutic potential of monoamine oxidase inhibitors. Nat Rev Neurosci 7:295e309.
23. Edmondson DE, Mattevi A, Binda C, Li M, Hubalek F. Structure and mechanism of monoamine oxidase. Curr Med Chem. 2004; 11:1983–1993. [PubMed: 15279562]
24. Edmondson DE, DeColibus L, Binda C, Li M, Mattevi A. New insights into the structures and functions of human monoamine oxidases A and B. J Neural Transm. 2007; 114:703–705. [PubMed: 17393064]
25. Saura JL, Cesure JM, Da Prada AM, Chan-Palay M, Huber V, Loffler G, Richard JG (1994) Neuroscience. 62 : 15e30.
26. Bortolato M, Chen K, Shih AS (2008) Monoamine oxidase inactivation: from pathophysiology to therapeutics. Ad. Drug Deliv Rev 60: 1527e1533.
27. Da Prada M, Zürcher, G; Wüthrich, I, Haefely, W EJ (2002) Neural Transm. 26, 31
28. Binda C, Newton-vinson P, Hubálek F, Edmondson DE, Mattevi A (2002) Structure of human monoamineoxidase B, a drug target for the treatment of neurological disorders. Nature Structural Biology 9: 22-26.
29. De Colibus L, Li M, Binda C, Lustig A, Edmondson DE, Mattevi A (September 2005).
30. "Three-dimensional structure of human monoamine oxidase A (MAO A): relation to the structures of rat MAO A and human MAO B" Proc Natl Acad Sci U S A. 2005 Sep 6; 102(36): 12684–12689.
31. S.Y. Son, J. Ma, Y. Kondou, M. Yoshimura, E. Yamashita, T. Tsukihara, Structure of human monoamine oxidase A at 2.2-_A resolution: the control of opening the entry for substrates/inhibitors, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 5739e5744.
32. J.L. Saura, J.M. Cesure, A.M. Da Prada, M. Chan-Palay, V. Huber, G. Loffler, J.G. Richard, Neuroscience 62 (1994) 15e30.
33. Chapman, A.G.; Hart, G.P. Anticonvulsant drug action and regional neurotransmitter amino acid changes. *J. Neural Transm*. **1988**, *72*, 201–212.

34. Silverman, R.B.; Nishimura, K.; Lu, X. Mechanism of inactivation of monoamine oxidase-B by the anticonvulsant agent milacemide (2-(n-pentylamino)acetamide). *J. Am. Chem. Soc.* **1993**, *115*, 4949–4954.
35. Wei Shen, Shian Yu, Jiaming Zhang, Weizheng Jia and Qing Zhu. Synthesis and Biological Evaluation of 2-Phenoxyacetamide Analogues, a Novel Class of Potent and Selective Monoamine Oxidase Inhibitors. *Molecules* **2014**, *19*, 18620-18631; doi:10.3390/molecules191118620.
36. Sliwoski, G. et al. (2014) Computational Methods in Drug Discovery. Pharmacol. Rev. 66, 334–395.
37. Banks MN, Houston JG. High throughput screening for lead discovery. In: Donald JA, ed. Burger's Medicinal Chemistry, Drug Discovery and Development. 6th Ed. USA: Wiley Publications, 2010: 38-67.
38. Borman S. New QSAR techniques eyed for environmental assessments. Chem Eng News 1990; 68: 20-23.
39. Hansch C, Leo A, Mekapati SB, et al. QSAR and ADME. Bioorg Med Chem 2004; 12: 3391–3400.
40. Kohli DV, Sharma MC, Sahu NK, et al. 2D-QSAR studies of some 1, 3, 4-thiadiazol-2-yl-azetidin-2-one as antimicrobial agents. Dig J Nano Biostru 2009; 4: 339-347.
41. Hansch C (1969) A quantitative approach to biochemical structure activity relationships. Acc Chem Res 2: 232-2

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